Middlesex University London

Middlesex University Research Repository

An open access repository of

Middlesex University research

http://eprints.mdx.ac.uk

Nouwen, Arie ORCID logoORCID: https://orcid.org/0000-0002-0609-4082, Adriaanse, M. C., van Dam, Kristina, Iversen, M. M., Viechtbauer, W., Peyrot, M., Caramlau, I., Kokoszka, A., Kanc, K., de Groot, M., Nefs, G. and Pouwer, F. (2019) Longitudinal associations between depression and diabetes complications: a systematic review and meta-analysis. Diabetic Medicine, 36 (12) . pp. 1562-1572. ISSN 0742-3071 [Article] (doi:10.1111/dme.14054)

Final accepted version (with author's formatting)

This version is available at: https://eprints.mdx.ac.uk/26914/

Copyright:

Middlesex University Research Repository makes the University's research available electronically.

Copyright and moral rights to this work are retained by the author and/or other copyright owners unless otherwise stated. The work is supplied on the understanding that any use for commercial gain is strictly forbidden. A copy may be downloaded for personal, non-commercial, research or study without prior permission and without charge.

Works, including theses and research projects, may not be reproduced in any format or medium, or extensive quotations taken from them, or their content changed in any way, without first obtaining permission in writing from the copyright holder(s). They may not be sold or exploited commercially in any format or medium without the prior written permission of the copyright holder(s).

Full bibliographic details must be given when referring to, or quoting from full items including the author's name, the title of the work, publication details where relevant (place, publisher, date), pagination, and for theses or dissertations the awarding institution, the degree type awarded, and the date of the award.

If you believe that any material held in the repository infringes copyright law, please contact the Repository Team at Middlesex University via the following email address:

eprints@mdx.ac.uk

The item will be removed from the repository while any claim is being investigated.

See also repository copyright: re-use policy: http://eprints.mdx.ac.uk/policies.html#copy

Running Title: Depression and diabetes complications

Longitudinal Associations Between Depression And Diabetes Complications: A Systematic Review And Meta-Analysis

Arie Nouwen[1], Marcel Adriaanse[2], Kristina van Dam[1], Marjolein M. Iversen[3], Wolfgang Viechtbauer[4], Mark Peyrot[3,5], Isabela Caramlau[6], Andrzej Kokoszka[7], Karin Kanc[8], Mary de Groot[9], Giesje Nefs[10,11,12], François Pouwer[13,14], for the European Depression in Diabetes (EDID) Research Consortium

[1]Middlesex University, London, UK; [2]Vrije Universiteit, Amsterdam, the Netherlands; [3]Western Norway University of Applied Sciences, Bergen, Norway; [4]Maastricht University, Maastricht, The Netherlands; [5]Loyola University Maryland, Baltimore, USA; [6]Beaumont Hospital, Dublin, Ireland; [7]Medical University of Warsaw, Poland; [8]Jazindiabetes (Diabetes&Me), Private Diabetes Centre, Ljubljana, Slovenia, [9]Indiana University School of Medicine, Indianapolis, USA, [10]Tilburg University, The Netherlands, [11]Radboud University Medical Center, Nijmegen, The Netherlands and [12] Diabeter, Rotterdam, The Netherlands; [13]University of Southern Denmark, Odense, Denmark and [14] STENO Diabetes Center Odense, Odense, Denmark.

All correspondence to Prof. Arie Nouwen, Middlesex University, The Burroughs, Hendon, London, UK, NW4 4BT. Email: a.nouwen@mdx.ac.uk

Word count

Abstract: 230

Main text: 3305

Conflict of interest. No potential or existing conflicts of interest relevant to this article were reported.

NOVELTY STATEMENT

1. Numerous studies have examined the longitudinal relationship between depression and diabetes complications but comprehensive evidence about the magnitude and direction is unavailable.
2. The current study shows that the relationship between depression and diabetes complications appears bi-directional with depression being associated with an increased risk of developing incident macrovascular and microvascular complications, and diabetes complications increasing the risk of subsequent depression.
3. The increase in risk of developing diabetes complications in depressed people (by 38% and 33% for macrovascular and microvascular complications, respectively) is higher than the increase in risk of developing depression (by 9% and 24% for macrovascular and microvascular complications, respectively) in people with diabetes complications.

Word count 109

ACKNOWLEDGMENTS

The authors thank Vicky Wallace of the Barnes Library, University of Birmingham, U.K., for help with the literature searches.

ABSTRACT

Aims. To conduct a systematic review and meta-analysis of longitudinal studies assessing the bi-directional association between depression and diabetes macrovascular and microvascular complications.

Methods. Embase, Medline, and PsycINFO databases were searched from inception through 27th November 2017. A total of 4,592 abstracts were screened for eligibility. Meta-analyses used multilevel random/mixed-effects models. Quality was assessed using the Newcastle-Ottawa scale.

Results. 22 studies were included in the systematic review. 16 studies examined the relationship between baseline depression and incident diabetes complications, of which nine studies involving over 1 million participants were suitable for meta-analysis. Depression was associated with an increased risk for incident macrovascular (Hazard Ratio HR=1.38; 95%CI: 1.30-1.47) and microvascular disease (HR=1.33; 95%CI: 1.25-1.41). Six studies examined the association between baseline diabetes complications and subsequent depression, of which two involving over 230 000 participants were suitable for meta-analysis. The results showed that diabetes complications increased the risk of incident depressive disorder (HR=1.14; 95%CI: 1.07-1.21). The quality analysis showed increased risk of bias notably in the representativeness of selected cohorts and ascertainment of exposure and outcome.

Conclusions. Depression in people with diabetes is associated with an increased risk of incident macrovascular and microvascular complications. The relationship between depression and diabetes complications appears bi-directional. However, the risk of developing diabetes complications in depressed people is higher than the risk of developing depression in people with diabetes complications. The underlying mechanisms warrant further research.

Key words: Type 1 Diabetes, Type 2 Diabetes, Depression, Diabetes complications, Systematic review, Meta-analysis

Introduction

Diabetes mellitus is associated with long-term complications including microvascular and macrovascular disease. Prospective studies have also shown a significant bi-directional relationship between type 2 diabetes and depression.[1,2] Meta-analytic evidence of longitudinal studies indicates that diabetes increases the risk of developing depression by approximately 25%,[3,4] and that depression increases the risk of incident type 2 diabetes by 40-60%.[2,3]

Depression not only increases emotional suffering among people with diabetes, it also is associated with elevated prevalence of diabetes complications.[5,6] More specifically, a meta-analysis of 27 studies focusing on the associations of depression with macrovascular complications (such as coronary artery disease), microvascular complications (diabetic retinopathy, neuropathy, nephropathy or end stage renal disease), and sexual dysfunction found a significant and consistent positive relationship.[7] Effect sizes (correlations) were small to moderate, ranging between 0.17 and 0.32 (overall effect size of 0.25) and were similar across type 1 and type 2 diabetes study samples. However, all included studies had a cross-sectional design, precluding the identification of directions and pathways. For example, similar to the longitudinal relationship between depression and diabetes, depression and diabetes complications may be related either bi-directionally (depression may increase the risk of incident diabetes complications and vice versa) or only uni-directionally.

Since the publication of that meta-analysis, a number of prospective population-based studies have examined the longitudinal relationships between depression and diabetes complications. However, comprehensive analysis of the magnitude and direction of these relationships is unavailable. Therefore, the aim was to examine the directional relationships between depression and diabetes macrovascular and microvascular complications by conducting a systematic review of longitudinal epidemiological studies. Where possible, meta-analyses were carried out to quantify the size of the associations.

METHODS

Data Sources and Searches

This study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[8] Literature searches were conducted using Embase, Medline and PsycInfo from inception through 27th November 2017, including references of eligible articles. Databases were searched using Medical Subject Headings (MeSH) and Boolean operators. The search terms (for Embase see Supplementary Text 1) were adapted to meet the requirements of each database.

Study Selection

The results of the searches were divided into batches of 500, and for each batch two authors independently screened the titles and abstracts. Selected papers were retrieved and two other authors independently scrutinised the full text papers for inclusion. Disagreements were solved by discussion between the authors and the first author (AN).

Articles meeting the following study criteria were included: a) involving adults (over 18 years old) at the time of follow-up with type 1 or type 2 diabetes mellitus; b) published in peer-reviewed, English language journals; c) examining the longitudinal relationship between depression and at least one long-term complication of type 1 or type 2 diabetes. Diabetes complications included microvascular diseases (retinopathy, neuropathy, nephropathy, sexual dysfunction or diabetic foot) and macrovascular diseases (angina, stroke, coronary artery disease, myocardial infarction, or peripheral vascular disease). Studies solely focusing on amputations related to diabetes complications (k=7) and studies examining the relationship between depression, diabetes and cardiovascular mortality were not included as these have been the topic of recent systematic review/meta-analyses.[9,10] Moreover, amputations reflect treatment decisions, which may confound their relationship with depression. Studies were also excluded if they focused on gestational diabetes, impaired glucose tolerance, or pre-diabetes. Studies examining the relationship of diabetes complications with either lifetime or current depression were included.

Data Extraction and Quality Assessment

One author (AN) performed data extraction, which was verified by two other authors (MA, MI). Data of interest included: 1) name of first author; 2) publication year; 3) country; 4) study design; 5) number of participants; 6) mean age/age range; 7) gender; 8) diabetes type; 9) diabetes duration; 10) follow–up length; 11) depression assessment method; 12) diabetes assessment method; 13) diabetes complications assessment method; 14) results regarding associations between depression and diabetes complication(s).

Method of depression assessment could be either a diagnosis of depression assessed by a diagnostic psychiatric interview or assessment of depressive symptoms using a self-report questionnaire. Type of diabetes and diabetes complications could be assessed either via self-report or extracted from medical records. Diabetes complications could be assessed either via self-report, or with the use of diagnostic tests, or extracted from medical records.

Quality assessment of included studies was conducted by two authors (AN, KvD) based on the Newcastle-Ottawa scale[11] for cohort studies. Three domains were evaluated for each study: selection of the study groups, comparability of the groups and ascertainment of outcome of interest (see Table 1). There were three levels of evidence: low risk of bias (a score of 7-9), moderate risk of bias (5-6), and high risk of bias (score < 5).[12]

Data Synthesis and Analysis

The meta-analysis used multilevel random/mixed-effects models with random effects for studies and estimates within studies, which accounts for the dependency in the underlying true effects for studies supplying multiple estimates (in some studies, the same participants were assessed for multiple macrovascular and microvascular outcomes). Although correlation in the sampling errors is not automatically considered in this model, theoretical considerations and simulation studies[13] have shown that the multilevel model automatically subsumes this source of dependency into the correlation between the true effects and therefore provides valid inferences about the fixed effects. As a sensitivity analysis, we also used cluster-robust inference methods[13,15] which yielded identical conclusions.

Criteria for meta-analysis were outcomes reported as proportional hazard ratios (HR) and 95% confidence intervals (95%CI). For some studies, to obtain the estimate of interest (e.g. reference group people with diabetes and no depression versus people with diabetes and depression), we recalculated HR using the procedures described in Van Dooren et al.[9] For Black et al.[16] we combined the HR for the group of participants with diabetes without any depressive symptoms (CES-D=0) and those with diabetes with minimal depression (CES-D=1-15) into the reference group. For Lin et al.,[17] we combined the groups with probable minor depression (PHQ-9 algorithm) and no depression into the reference group and compared them with the group with probable major depression (PHQ-9 algorithm). For Scherrer et al.,[18] we used the information from the four-group scenario (neither diabetes nor MDD, MDD alone, type 2 diabetes alone, and comorbid MDD and type 2 diabetes) to obtain the HR for the comparison of the two diabetes groups. For the meta-analyses, all outcome variables were dichotomized.

RESULTS

Search results

Figure 1 shows the results of the selection process. The searches yielded 7,457 potential articles. After removing conference papers, books, dissertation abstracts and duplicates within or between the databases, 4,591 abstracts remained. Twenty-nine eligible papers were selected, 24 from EMBASE and 5 additional papers from Medline (no additional papers from PsycInfo). One of the authors identified an additional paper[19] not included in the search results, bringing the total to 30 papers. Searches of the reference lists did not identify additional potential papers. The extracted data of the 30 studies are presented in Supplementary Tables 1a-1c.

Where more than one study relied on the same cohort [six papers from the Epidemiological Diabetes Cohort (EDC) Study,[20–25] four from the Pathways Epidemiological Study[17,26–28]], only the most recent or the most complete study[17,23] was selected for the review, resulting in 22 papers being included in the systematic review. Of those, 16 papers including 1,025,563 people with diabetes examined the relationship of depression to incident diabetes complications (see Supplementary

Tables 1a,b), while six studies including 239,519 people with diabetes examined the relationship of diabetes complications to incident depression (see Supplementary Table 1c). Data came predominantly from the USA but also from Canada, China, Italy, Norway, Taiwan, Germany, UK, and the Netherlands.

Three of the 22 studies examined people with type 1 diabetes mellitus,[23,29,30] nine examined people with type 2 diabetes mellitus,[16-19,32–36], and six studies examined people with either type of diabetes mellitus.[31,37–41] Four studies did not specify the type of diabetes.[42–45]

Twelve studies quantified the results in terms of Cox proportional hazard ratios[16-19,31–34,38,41,42,45], others used odds ratios,[29,30,36,40,43,44] relative risk[37], or provided regression coefficients.[39] Two papers briefly explained that depression did not increase incident diabetes complications but did not report the numerical details.[23,35] Of the 12 studies reporting Cox proportional hazard ratios, 10 studies concerned depression as a risk factor for the onset of diabetes complications and two studies concerned the relationship from diabetes complications to incident depression.

Depression as a risk factor for diabetes complications

Finally, nine studies of the ten studies reporting HR and 95% CI were suitable for meta-analysis; one study was not suitable for inclusion because a continuous depression measure was used rather than dichotomised depression.[41] Nine studies allowed for a meta-analysis testing depression as a risk factor for macrovascular disease. Four of the nine studies had provided data on depression as a risk factor for microvascular complications, which could be used in an additional meta-analysis. Of the nine studies[16-19,31–33,38,45], most used a composite macrovascular outcome including conditions such as myocardial infarction, coronary artery disease, congestive heart failure, stroke, but some also included cardiovascular procedures (e.g. percutaneous coronary artery intervention, coronary artery bypass grafting, abdominal aortic aneurysm repair, and revascularization of the lower extremity[16]) or unstable angina[32] to obtain a single estimate of macrovascular disease. However, one study[31] reported separate outcomes for stroke and coronary heart disease for the same sample, which were included individually.

Of the four studies also analyzing microvascular complications,[16,17,31,32] three studies included a composite microvascular outcome,[16,17,32] while Novak et al.[31] only used incident chronic kidney disease as an outcome.

To examine whether the HR of developing complications in people with diabetes and depression differed according to the type of complication (macro/micro), we first carried out a moderator analysis. The results showed that the relation between depression and complication development did not differ according to type of complication [$\chi^2(1)=0.67$, $p=0.41$], allowing us to analyse an overall measure of complications.

In this initial analysis, those with depression were on average 51% more likely to develop a complication than those without depression (HR=1.51; 95%CI: 1.23-1.86). A forest plot of the HR and 95%CI of each study, together with the estimated overall HR based on all estimates combined, is shown in Fig. 2.

However, there was considerable heterogeneity between studies [Cochran's $Q(13)=92.30$, $p<0.001$; $I^2=86\%$]. Standardized residuals and Cook's distances showed that Black et al.[16] was an influential study and the source of the heterogeneity in these data (primarily due to a much larger effect size than other studies for microvascular disorders). This study was also the only study in the initial meta-analysis where complications were based on self-report; *therefore, we repeated the above analyses without its inclusion and regard these results as our study's primary findings.*

Moderator analysis of complication type was significant for these 11 studies [$\chi^2(1)=18.82$, $p<0.001$]; therefore results are reported separately for macrovascular and microvascular complications. Depression was associated with an increased risk of macrovascular (HR=1.38; 95%CI: 1.30-1.47) and microvascular (HR=1.33; 95%CI: 1.25-1.41) complications (see Fig. 2). Sensitivity analyses using the cluster-robust inference approach yielded identical conclusions in all analyses reported above.

A number of studies (k=7) identified in the systematic review reported incompatible statistics and could not be included in the meta-analysis (e.g. odds ratios instead of hazard ratios; for details, see

Supplementary Table 1). In terms of macrovascular complications, results of two studies supported the findings of the meta-analysis.[29,36] Another study[23] found a significantly increased risk only for angina (HR=1.40; 95%CI: 1.06-1.84), but not for objective CAD (no statistics were provided for the latter). In terms of microvascular complications, results were mixed, with three studies supporting[30,41,43] and two failing to support the findings of the meta-analysis.[35,36] Regarding incident foot ulcers, one study found that there was a linear relationship between increased risk and severity of depressive symptoms.[43]

Diabetes complications as a risk factor for depression

Six studies examined the hypothesis that diabetes complications increase the risk of incident depression.[34,37,39,40,42,44] For the two largest of these studies (combined N = 234,628) nine HRs of diagnosed depression were suitable for meta-analysis.[34,42] Therefore, we tested whether any diabetes complication increased the risk of incident depressive disorder. Therefore, we tested whether any diabetes complication increased the risk of incident depressive disorder. Results showed that diabetes complications increased the risk of incident depressive disorder (HR=1.14; 95%CI: 1.07-1.21). Analysis using the cluster-robust approach confirmed these results. Because moderator analysis of complication type was significant [$\chi^2(1)=3.91$, p=.048], we report the results of the meta-analysis separately for macrovascular and microvascular complications. Both macrovascular complications (HR=1.09; 95%CI: 1.02-1.17) and microvascular complications (HR=1.24; 95%CI: 1.12-1.37) were associated with an increased risk of depressive disorder.

For a Forest plot, see Fig. 3.

The remaining four studies[37,39,40,44] reported statistics incompatible with their inclusion in the meta-analysis (e.g. odds ratios or relative risks instead of hazard ratios; for details, see Supplementary Table 1-c). One study[44] found that diabetes complications (not specified) increased the odds of developing depressive symptoms (OR=1.46 (95%CI 1.14–1.86). The results of the three studies that did look at specific diabetes complications mimicked those of the two studies in the meta-analyses. Regarding macrovascular complications, one study[37] found an increased risk of depressive

symptoms with coronary artery disease, cerebral vascular disease and peripheral vascular disease, while another study[40] found this to be the case for macrovascular events or procedures but not for stroke. Regarding microvascular complications, one study[40] found no significant increased risk of depressive symptoms with either retinopathy or nephropathy. Two other studies[37,39] found an increased risk of depressive symptoms with neuropathy, but not with retinopathy or foot problems[37]. For details, see Supplementary Table 1c).

Quality of evidence

Of the 22 included studies, two showed high risk of bias, eight showed moderate risk of bias and 12 showed low risk of bias (see Table 1). Risk of bias was mainly due to the use of selected rather than representative cohorts (8/22 studies), use of self-report or failure to report use of secure records or structured interviews to ascertain exposure (15/22 studies) or outcome (9/22 studies), and failure to demonstrate that the outcome of interest (diabetes complications/depression) was not present at baseline (10/22 studies, although all but three studies[36,38,45] statistically controlled for this).

DISCUSSION

This systematic review identified nine studies suitable for meta-analysis which showed that in people with diabetes, those with co-morbid depression have a 38% and 33% increase in risk of developing macrovascular and microvascular complications, respectively, compared to controls without depression. The systematic review also identified eight studies unsuitable for inclusion in the meta-analysis. For macrovascular complications, results of these studies generally concurred with those obtained in the meta-analysis, except for one study.[23] For microvascular complications, results were mixed, with three studies supporting[30,41,43] and two failing to support[35,36] the findings of meta-analysis. Of the latter, one examined participants during their first two years of newly diagnosed diabetes,[36] and the other had cognitive function as the main predictor variable.[35]

Finally, six identified studies examined the relationship from diabetes complications to incident depression.[34,37,39,40,42,44] In the meta-analysis of the two largest studies[34,42] (total N = 234,628) diabetes complications increased the risk of developing depressive disorder by 14%. Although this

increase in risk was found to be higher for microvascular complications than for macrovascular complications (by 24% vs 9%, respectively), because of the small number of studies these results should be interpreted with caution. The results of the six studies not included in the meta-analyses (Supplementary Table 1c) mimic those of the meta-analysis and suggest that having macrovascular and microvascular diabetes complications may increase the risk of developing depression. However, across the six studies examining the relationship of diabetes complication as a risk factor for depression, we did not find evidence of a systematic effect of specific complications.

Taken together our results provide support for a bi-directional relationship between diabetes complications and depression. In other words, depression (both depressive symptoms and major depressive disorder) increases the risk of incident macrovascular and microvascular diabetes complications, and the presence of diabetes complications increases the risk of significant depressive symptoms and/or possible depressive episode. However, the increase in risk of developing diabetes complications (by 38% and 33% for macro and micro-vascular complications, respectively) in depressed people is higher than the increase in risk of developing depression (by 9% and 24% for macro and micro-vascular complications, respectively) in people with diabetes complications. These findings parallel those found for the bi-directional longitudinal relationships between diabetes and depression with a modest increased relative risk (15%) of developing depression in people with diabetes and a higher relative risk (60%) for the development of diabetes in depressed people.[2]

These findings may reflect different underlying mechanisms for the relationship from depression to diabetes or diabetes complications than for the relationship from diabetes or diabetes complications to depression. While the exact nature of these underlying mechanisms remains unknown, there are a number of common processes that may result in these negative outcomes. First, depression is often accompanied by behavioural changes including reduced self-care and medication adherence[46], increased smoking, reduced physical activity and increased sedentary behaviours, and increased intake of high calorie food.[47] These behaviours may be particularly problematic in the context of

diabetes and are likely to adversely affect glycaemic control, which, in turn is associated with increased risk of complications[48]. Moreover, the UKPDS has shown that a 1% in reduction in HbA1c may delay the onset of diabetes complication by 21%.[49] However, studies found no evidence that depression delays insulin initiation.[50,51]

More recently, biological processes associated with obesity, insulin resistance, and persistent poor glucose control have been implicated in the development of diabetes complications in the context of depression. More specifically, inflammatory processes associated with both diabetes and depression[52] have been identified as possible mechanisms.[53] Other studies have shown that depression and diabetes is associated with endothelial function, increasing the risk of macrovascular disease[54] although underlying mechanisms are yet to be elucidated.

The mechanisms underlying the increased risk of incident depression as a result of diabetes complications are likely to be similar to those hypothesised for diabetes as a risk for depression onset. Although inflammation and other biological factors may play a role,[52,54] the epidemiological evidence points to the role of diabetes burden and distress as contributing factors.[55,56] The results of our study showing no systematic effect of specific diabetes complications is consistent with the latter. It should be noted that only one study[39] examining the relationship of complications with incident depression controlled for pain as a possible contributor.

Overall, the results of the current study extend the findings of a previous systematic review/meta-analysis of cross-sectional studies[7] and shows that depression is associated with increased risk of diabetes complications. Importantly, given that depression is a treatable condition, the clinical implication of this study is that depression could be a preventable risk factor for diabetes complications. Future studies are needed to examine whether intensive and successful treatment of depression in diabetes does indeed reduce the risk of future complications.[57]

The current study also adds to an increasing number of longitudinal studies showing that depression in diabetes, even when using self-report questionnaires, can have serious consequences including reduced self-care,[39] increased cognitive decline,[58] dementia,[59] and mortality.[9]

A number of limitations should be taken into consideration when interpreting the results of this study. First, despite the large number of participants on which the meta-analyses were based, the relatively small number of studies available (*k*=9 for the relationship from depression to diabetes complications and *k*=2 for the relationship from diabetes complications to depression) precluded examination of the contribution of factors such as specific diabetes complications, type of depression measurement, and type of diabetes. Moreover, although some studies included participants with type 1 diabetes with paediatric onset, teasing out the effects of depression on diabetes complications in type 1 versus type 2 diabetes remains a topic for future research. Second, the quality assessment of the included studies found high risk of bias in two studies due to, among other factors, the use of self-report measures to ascertain exposure or outcome. Self-report should be avoided when objective diagnostic tests are available, such as in the case of diabetes complications. However, as there are no known biomarkers for depression, its assessment remains based on symptomatology; although structured diagnostic interviews are considered the gold standard for identifying depression, self-report symptom questionnaires are commonly used. While the use of questionnaires may be considered as introducing bias, research suggests that symptom questionnaires and diagnostic interviews assess different constructs, with elevated depressive symptoms more reflective of general and diabetes-specific emotional distress than of clinical depression.[60] Furthermore, although most studies provided follow-up data, only a few studies provided information as to how many people had died from diabetes complications during the follow-up period. Because mortality is higher in people with depression, it is likely that the results from the meta-analysis are conservative. Third, the included studies did not provide information regarding the specific set of complications individuals developed during the study. It is therefore impossible to ascertain whether depression leads to the development of only single complications or a cluster of complications. Furthermore, some of the studies in the meta-analysis[17,31–33] included not only diabetes complications but also surgical interventions, which may or may not have resulted from the onset or worsening of diabetes complications and may have confounded the observed

relationships. Fourth, it is unclear how clinical management, access to medical care, disease management supplies and medications, financial burden of diabetes, and other socioeconomic factors play into the development of depression or diabetes complications and the relationship between the two.

In summary, depression in people with diabetes is associated with an increased risk of incident macrovascular and microvascular complications. This relationship is likely to be bi-directional as diabetes complications were also found to increase the risk of incident depression. It remains to be determined whether effective treatment of depression reduces the risk of developing diabetes complications.

FUNDING
There was no funding source for this study.

Author contributions. All authors researched abstracts, had opportunities to interpret results and critically review the manuscript. In addition, AN did literature searches, extracted the data, drafted the report; MA extracted and harmonised the data, interpreted the results, contributed to the discussion, edited and revised the manuscript; KvD harmonised the data, carried out the quality of evidence analysis, revised the manuscript; MMI extracted and harmonised the data, revised the manuscript and contributed to the discussion; WV carried out the meta-analysis, edited and revised the manuscript; MP contributed to the discussion, and critically revised and edited the manuscript; IC designed the search strategy; MdG reviewed and revised the manuscript; GN analysed the data, interpreted the results, contributed to the discussion, and edited and revised the manuscript; FP interpreted the results, contributed to the discussion, and edited and revised the manuscript. AN is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for its integrity

REFERENCES

1. Golden SH. Examining a Bidirectional Association Between Depressive Symptoms and Diabetes. *JAMA*. 2008;**299**(23):2751-2759.
2. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: A meta-analysis. *Diabetes Care*. 2008;**31**(12):2383-2390.
3. Rotella F, Mannucci E. Depression as a risk factor for diabetes: a meta-analysis of longitudinal studies. *J Clin Psychiatry*. 2013;**74**(1):31-37.
4. Nouwen A, Winkley K, Twisk J, Lloyd CE. Type 2 diabetes mellitus as a risk factor for the onset of depression : a systematic review and meta-analysis. *Diabetologia*. 2010;**53**(12):2480-2486.
5. Lustman PJ, Clouse RE. Depression in diabetic patients: The relationship between mood and glycemic control. *J Diabetes Complications*. 2005;**19**(2):113-122.
6. van Steenbergen-Weijenburg KM, van Puffelen AL, Horn EK, Nuyen J, van Dam PS, Beekman AT, et al. More co-morbid depression in patients with Type 2 diabetes with multiple complications. An observational study at a specialized outpatient clinic. *Diabet Med*. 2011;**28**(1):86-89.
7. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression

and diabetes complications: a meta-analysis. *PsychosomMed*. 2001;**63**(4):619-630.
8. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 2009;**6**(7): e1000097.
9. Van Dooren FEP, Nefs G, Schram MT, Verhey FRJ, Denollet J, Pouwer F. Depression and Risk of Mortality in People with Diabetes Mellitus: A Systematic Review and Meta-Analysis. *PLoS One*. 2013;**8**(3):e57058.
10. O'Neill, Kabir, McNamara, Buckley. Comorbid depression and risk of lower extremity amputation in people with diabetes: systematic review and meta-analysis. *BMJ Open Diabetes Res Care*. 2017;**5**(1):e000366.
11. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. *Ottawa Hosp Res Inst*. 2013;(3):1-4. doi:10.2307/632432.
12. McPheeters ML, Kripalani S, Peterson NB, Idowu RT, Jerome RN, Potter SA, et al. Closing the quality gap: revisiting the state of the science (vol. 3: quality improvement interventions to address health disparities). Evidence report/technology assessment. *Evid Rep Technol Assess (Full Rep).* 2012 Aug;(208.3):1-475.
13. Moeyaert M, Ugille M, Beretvas SN, Ferron J, Bunuan R, Van den Noortgate W. Methods for dealing with multiple outcomes in meta-analysis: A comparison between averaging effect sizes, robust variance estimation and multilevel meta-analysis. *International J Soc Res Methodol*. 2017;**20**(6):559-572.
14. Van den Noortgate W, Lopez-Lopez JA, Marin-Martinez F, Sanchez-Meca J. Meta-analysis of multiple outcomes: A multilevel approach. *Behav Res Methods*. 2015;**47**(4): 1274-1294.
15. Hedges LV, Tipton E, Johnson MC. Robust variance estimation in meta-regression with dependent effect size estimates. *Res Synth Methods*. 2010;**1**(1):39-65.
16. Black S, Markides K, Ray L. Depression Predicts Increased Incidence of Adverse Health Outcomes in Older Mexican Americans With Type 2 Diabetes. *Diabetes Care* 2003;**26**(10):2822-2828.
17. Lin EH, Rutter CM, Katon W, Heckbert SR, Ciechanowski P, Oliver MM, et al. Depression and Advanced Complications of Diabetes A prospective cohort study. *Diabetes Care.* 2010;**33**(2):264-269.
18. Scherrer JF, Garfield LD, Chrusciel T, Hauptman PJ, Carney RM, Freedland KE, et al. Increased risk of myocardial infarction in depressed patients with type 2 diabetes. *Diabetes Care*. 2011;**34**(8):1729-1734.
19. Nefs G, Pop VJM, Denollet J. Depressive Symptom Clusters Differentially Predict Cardiovascular Hospitalization in People With Type 2 Diabetes. *Psychosomatics*. 2015;**56**(6):662-673.
20. Lloyd CE, Kuller LH, Ellis D, Becker DJ, Wing RR, Orchard TJ. Coronary artery disease in IDDM. Gender differences in risk factors but not risk. *ArteriosclerThrombVascBiol*. 1996; **16**(6):720-726.
21. Fickley CE, Lloyd CE, Costacou T, Miller RG, Orchard TJ. Type A behavior and risk of all-cause mortality, CAD, and CAD-related mortality in a type 1 diabetic population: 22 years of follow-up in the Pittsburgh epidemiology of diabetes complications study. *Diabetes Care*. 2013;**36**(10):2974-2980.
22. Orchard TJ, Virella G, Forrest KY-Z, Evans RW, Becker DJ, Lopes-Virella MF. Antibodies to Oxidized LDL Predict Coronary Artery Disease in Type 1 Diabetes A Nested Case-Control Study From the Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes.*1999;**48**(7):1454-1458.
23. Orchard TJ, Olson JC, Erbey JR, Williams K, Forrest KY, Smithline Kinder L, et al. Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes: 10-year follow-up data from the Pittsburgh epidemiology of diabetes complications study. *Diabetes Care*. 2003;**26**(5):1374-1379.
24. Forrest KY, Becker DJ, Kuller LH, Wolfson SK, Orchard TJ. Are predictors of coronary

heart disease and lower-extremity arterial disease in type 1 diabetes the same? A prospective study. *Atherosclerosis*. 2000;**148**(1):159-169.
25. Kinder LS, Kamarck TW, Baum A, Orchard TJ. Depressive symptomatology and coronary heart disease in Type I diabetes mellitus: a study of possible mechanisms. *Health Psychol*. 2002;**21**(6):542-552.
26. Sieu N, Katon W, Lin EHB, Russo J, Ludman E, Ciechanowski P. Depression and incident diabetic retinopathy: A prospective cohort study. *Gen Hosp Psychiatry*. 2011;**33**(5):429-435.
27. Williams LH, Rutter CM, Katon WJ, Reiber GE, Ciechanowski P, Heckbert SR, et al. Depression and incident diabetic foot ulcers: A prospective cohort study. *Am J Med*. 2010;**123**(8):748-754.
28. Yu MK, Weiss NS, Ding X, Katon WJ, Zhou XH, Young BA. Associations between depressive symptoms and incident ESRD in a diabetic cohort. *Clin J Am Soc Nephrol*. 2014;**9**(5):920-928.
29. Roy MS, Peng B, Roy A. Risk factors for coronary disease and stroke in previously hospitalized African-Americans with Type 1 diabetes: A 6-year follow-up. *Diabet Med*. 2007;**24**(12):1361-1368.
30. Roy MS, Roy A, Affouf M. Depression is a Risk Factor for Poor Glycemic Control and Retinopathy in African-Americans With Type 1 Diabetes. *Psychosom Med*. 2007;**69**(6):537-542.
31. Novak M, Mucsi I, Rhee CM, Streja E, Lu JL, Kalantar-Zadeh K, et al. Increased risk of incident chronic kidney disease, cardiovascular disease, and mortality in patients with diabetes with comorbid depression. *Diabetes Care*. 2016;**39**(11):1940-1947.
32. Sullivan M, O'Connor P, Feeney P, Hire D, Simmons DL, Raisch DW, et al. Depression Predicts All-Cause Mortality. *Diabetes Care*. 2012;**35**:1708-1715.
33. Ting RZW, Lau ESH, Ozaki R, Lau WW, Kong AP, Luk AO, et al. High risk for cardiovascular disease in Chinese type 2 diabetic patients with major depression - A 7-year prospective analysis of the Hong Kong DiabetesRegistry. *J Affect Disord*. 2013;**149**(1-3):129-135.
34. Jacob L, Kostev K. Prevalence of depression in type 2 diabetes patients in German primary care practices. *J Diabetes Complications*. 2016;**30**(3):432-437.
35. Trento M, Charrier L, Salassa M, Merlo S, Passera P, Baltatescu A, et al. Cognitive function may be a predictor of retinopathy progression in patients with type 2 diabetes. *Eur J Ophthalmol*. 2017;**27**(3):278-280.
36. Ismail K, Moulton CD, Winkley K, Pickup JC, Thomas SM, Sherwood RA, et al. The association of depressive symptoms and diabetes distress with glycaemic control and diabetes complications over 2 years in newly diagnosed type 2 diabetes: a prospective cohort study. *Diabetologia*. 2017;**60**(10):2092-2102.
37. Deschênes SS, Burns RJ, Pouwer F, Schmitz N. Diabetes Complications and Depressive Symptoms. *Psychosom Med*. 2017;**79**(5):603-612.
38. Clouse R, Lustman P, Freedland K, Griffith L, McGill J, Carney R. Depression and coronary heart disease in women with diabetes. *Psychosom Med*. 2003;**65**(3):376-383.
39. Vileikyte L, Peyrot M, Gonzalez JS, Rubin RR, Garrow AP, Stickings D, et al. Predictors of depressive symptoms in persons with diabetic peripheral neuropathy: A longitudinal study. *Diabetologia*. 2009;**52**(7):1265-1273.
40. Katon WM, Russo JP, Lin EH, Heckbert SR, Ciechanowski P, Ludman EJ, Von Korff M. Depression and diabetes: factors associated with major depression at five-year follow-up. *Psychosomatics*. 2009;**50**(6):570-579.
41. Gonzalez JS, Vileikyte L, Ulbrecht JS, Rubin RR, Garrow AP, Delgado C, et al. Depression predicts first but not recurrent diabetic foot ulcers. *Diabetologia*. 2010;**53**(10):2241-2248.
42. Pan HH, Li CY, Chen PC, Lee MD, Liang CY, Hou WH, Wang KY. Contributions of diabetic macro-vascular complications and hip fracture to depression onset in elderly patients with diabetes: An 8-year population-based follow-up study. *J Psychosom Res*.

2012;**73**(3):180-184.
43. Iversen MM, Tell GS, Espehaug B, Midthjell K, Graue M, Rokne B, et al. Is depression a risk factor for diabetic foot ulcers? 11-years follow-up of the Nord-Trøndelag Health Study (HUNT). *J Diabetes Complications*. 2015;**29**(1):20-25.
44. Bell T, Dávila AL, Clay O, Markides KS, Andel R, Crowe M. The association between cognitive decline and incident depressive symptoms in a sample of older Puerto Rican adults with diabetes. *Int Psychogeriatrics*. 2017;**29**(8):1317-1325.
45. Jani BD, Cavanagh J, Barry SJE, Der G, Sattar N, Mair FS. Relationship Between Blood Pressure Values, Depressive Symptoms, and Cardiovascular Outcomes in Patients With Cardiometabolic Disease. *J Clin Hypertens*. 2016;**18**(10):1027-1035.
46. Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, Safren SA. Depression and diabetes treatment nonadherence: a meta-analysis. *Diabetes Care.* 2008;**31**:2398-2403.
47. Penninx BWJH. Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms. *Neurosci Biobehav Rev*. 2017;**74**:277-286.
48. Zoungas S, Chalmers J, Ninomiya T, Li Q, Cooper ME, Colagiuri S, et al. Association of HbA1c levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds. *Diabetologia*. 2012;**55**(3):636-643.
49. Stratton IM. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;**321**(7258):405-412.
50. Nefs G, The longitudinal association between depressive symptoms and initiation of insulin therapy in people with type 2 diabetes in primary care, *PLoS One*. 2013; **8**(11): e78865.
51. Iversen MM, Nefs G, Tell GS, Espehaug B, Midthjell K, Graue M, Pouwer F. Anxiety, depression and timing of insulin treatment among people with type 2 diabetes: Nine-year follow-up of the Nord-Trøndelag Health. *J Psychosom Res*. 2015; **79**(4): 309–315.
52. Laake JP, Stahl D, Amiel SA, Petrak F, Sherwood RA, Pickup JC, Ismail K. The Association Between Depressive Symptoms and Systemic Inflammation in People With Type 2 Diabetes: Findings From the South London Diabetes Study. *Diabetes Care*. 2014;**37**(8):2186-2192.
53. Fossati P, Radtchenko A, Boyer P. Neuroplasticity: From MRI to depressive symptoms. *Eur Neuropsychopharmacol*. 2004;**14**(SUPPL. 5):S503-S510.
54. van Agtmaal MJM, Houben AJHM, Pouwer F, Stehouwer CDA, Schram MT. Association of Microvascular Dysfunction With Late-Life Depression. *JAMA Psychiatry*. 2017;**74**(7):729-739.
55. Demakakos P, Zaninotto P, Nouwen A. Is the association between depressive symptoms and glucose metabolism bidirectional? Evidence from the English Longitudinal Study of Ageing. *Psychosom Med*. 2014;**76**(7):555-561.
56. Nouwen A, Nefs G, Caramlau I, Connock M, Winkley K, Lloyd CE, et al. Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: A systematic review and meta-analysis of the European Depression in Diabetes (EDID) research consortium. *Diabetes Care*. 2011;**34**(3):752-762.
57. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with diabetes mellitus: an abridged Cochrane review. *Diabet Med*. 2014;**31**(7):773-786.
58. Demakakos P, Muniz-Terrera G, Nouwen A. Type 2 diabetes, depressive symptoms and trajectories of cognitive decline in a national sample of community-dwellers: A prospective cohort study. *PLoS One*. 2017;**12**(4). e0175827.
59. Katon W, Pedersen HS, Ribe AR, Fenger-Grøn M, Davydow D, Waldorff FB, Vestergaard M. et al. Effect of Depression and Diabetes Mellitus on the Risk for Dementia. *JAMA Psychiatry*. 2015;**72**(6):612-619.
60. Fisher L, Skaff MM, Mullan JT, Arean P, Mohr D, Masharani U, et al. Clinical depression versus distress among patients with type 2 diabetes: Not just a question of semantics.

Diabetes Care. 2007;**30**(3):542-548.

Table 1. Results of quality assessment of studies identified in the systematic review, based on the Newcastle Ottawa- scale

	Selection				**Comparability**		**Outcome**			
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure (predictor - depression/complication)	Demonstration that outcome of interest was not present at start of study	Controlled for minimum: Complications/depression at baseline or excluded	Controlled for anything else	Assessment of outcome	Was follow-up long enough for outcome to occur	Adequacy of follow up of cohorts	Total Score
Acceptable	a, b	a, b	a, b	a	a	a	a, b	a	a, b	9
Depression to Diabetes Complications										
Black et al., 2003[16]	b	a	c	b	a	a	c	a	b	6
Clouse et al., 2003[38]	c	a	b	b	b	a	b	a	b	6
Orchard 2003[23]§	c	a	c	a	a	a	d	a	b	6
Roy et al, 2007a[29]♯	b	a	c	a	a	a	b	a	b	8
Lin et al., 2010[17]¶	b	a	c	b	a	a	b	a	b	7
Scherrer et al., 2011[18]	c	a	a	a	a	a	b	a	-	7
Sullivan et al., 2012[32]	d	a	c	b	a	a	d	b	d	3
Ting et al., 2013[33]	c	a	a	a	a	a	b	a	b	8
Nefs et al., 2015[19]	b	a	c	b	a	a	b	a	d	6
Novak et al, 2016[31]	c	a	a	a	a	a	b	a	b	8
Roy et al., 2007b[30]♯	b	a	c	a	a	a	a	a	b	8
Gonzalez et al., 2010[41]*	c	a	c	a	a	a	c	a	a	6
Iversen et al., 2015[43]	a	a	c	a	a	a	c	a	b	7
Jani et al., 2016[45]	b	a	c	b	b	a	b	b	-	4
Ismail et al., 2017[36]	b	a	c	b	b	a	b	b	b	5
Trento et al., 2017[35]	b	a	c	b	a	a	a	a	b	7
Diabetes Complications to Depression										
Katon et al., 2009[40]¶	b	a	a	b	a	a	c	a	b	7
Vileikyte et al., 2009[39]*	c	a	c	b	a	a	c	a	b	5
Pan et al., 2012[42]	b	a	a	a	a	a	a	a	d	8
Jacob & Kostev, 2016[34]	a	a	a	a	a	a	b	a	-	8
Bell et al., 2017[44]	b	a	c	a	a	a	c	a	b	7
Deschênes et al., 2017[37]	a	a	c	a	a	a	c	a	c	6

♯EPESE cohort
§ EDC cohort
¶ Pathways cohort
*Baltimore, State College and Manchester Hospital cohorts
- Retrospective analyses
For a summary and scoring of the Newcastle-Ottawa scales see Supplementary Text 2.

Figure legends

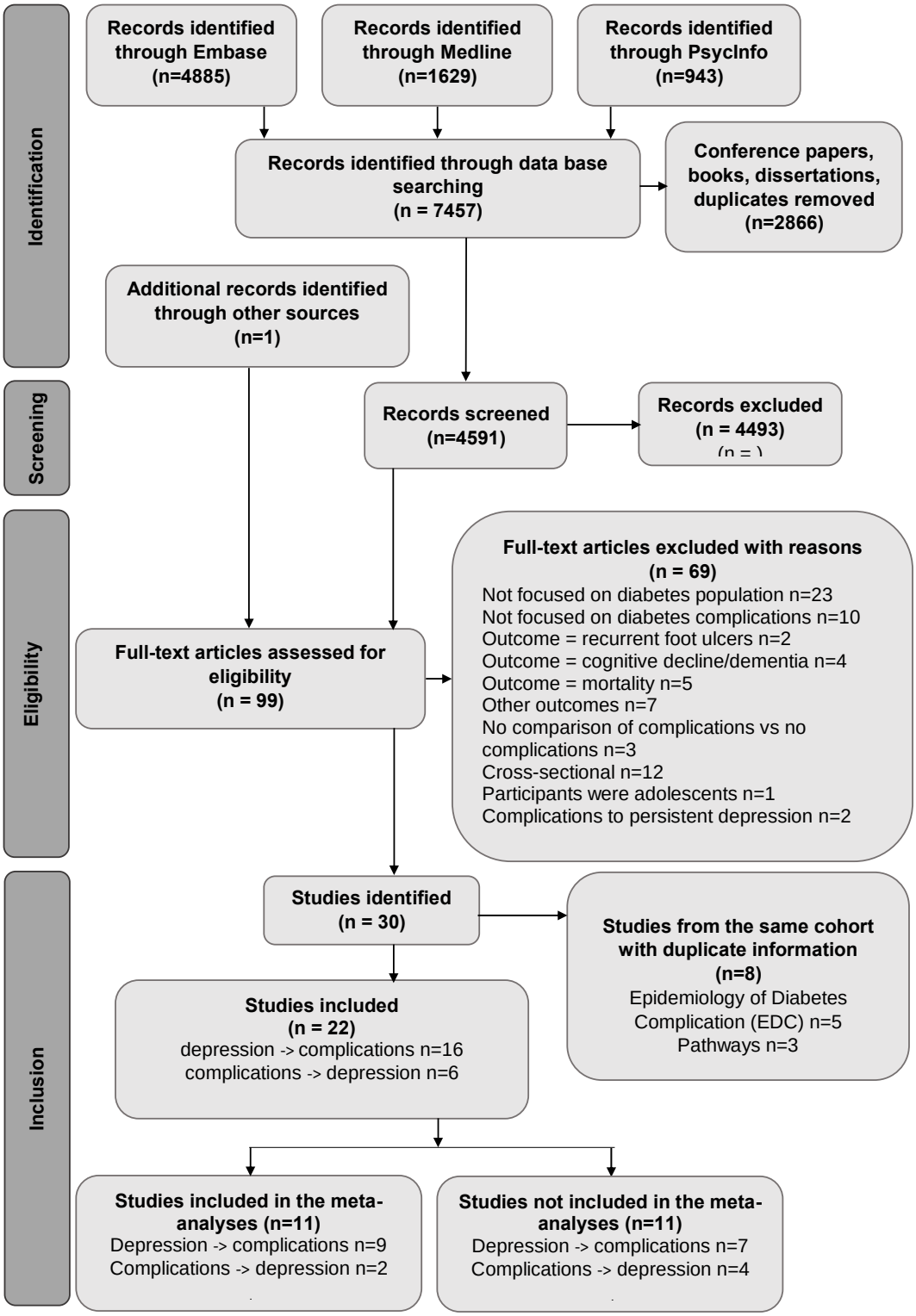
Figure 1. Flow chart of study selection process.

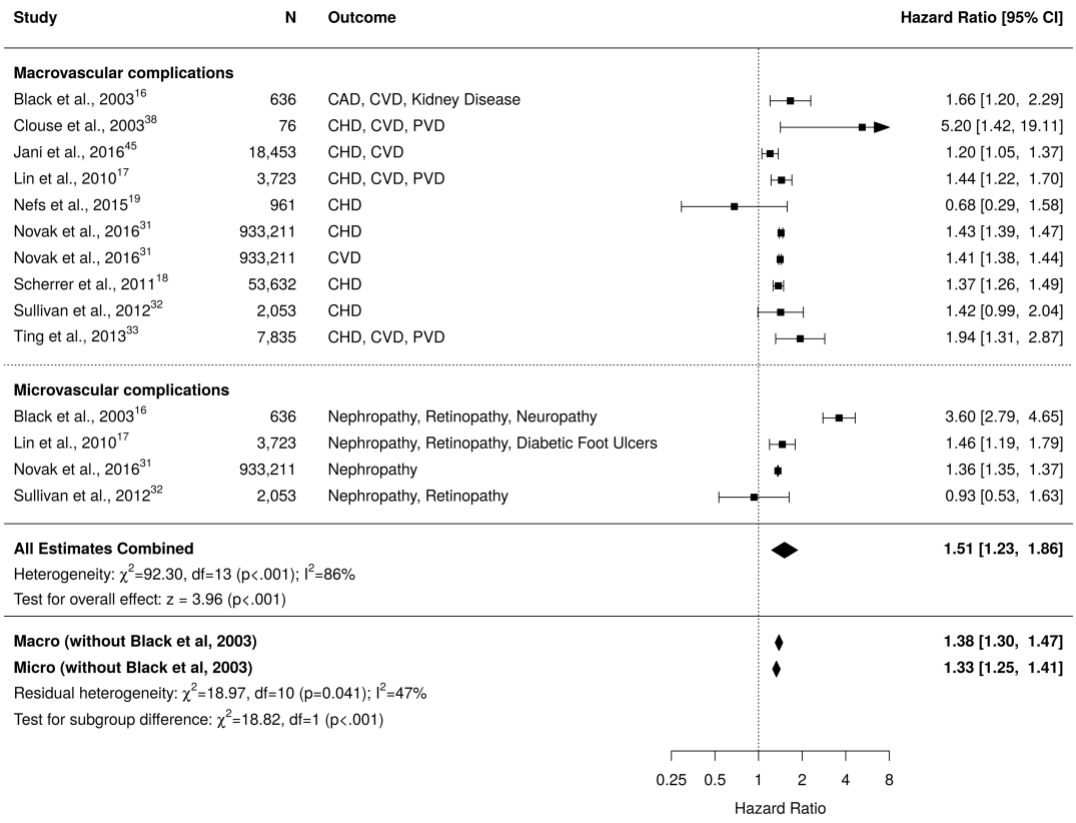
Figure 2. Forest Plot of hazard ratios of longitudinal studies included in the meta-analysis examining associations from baseline depression to incident diabetes complications, grouped by macrovascular complications and microvascular complications.

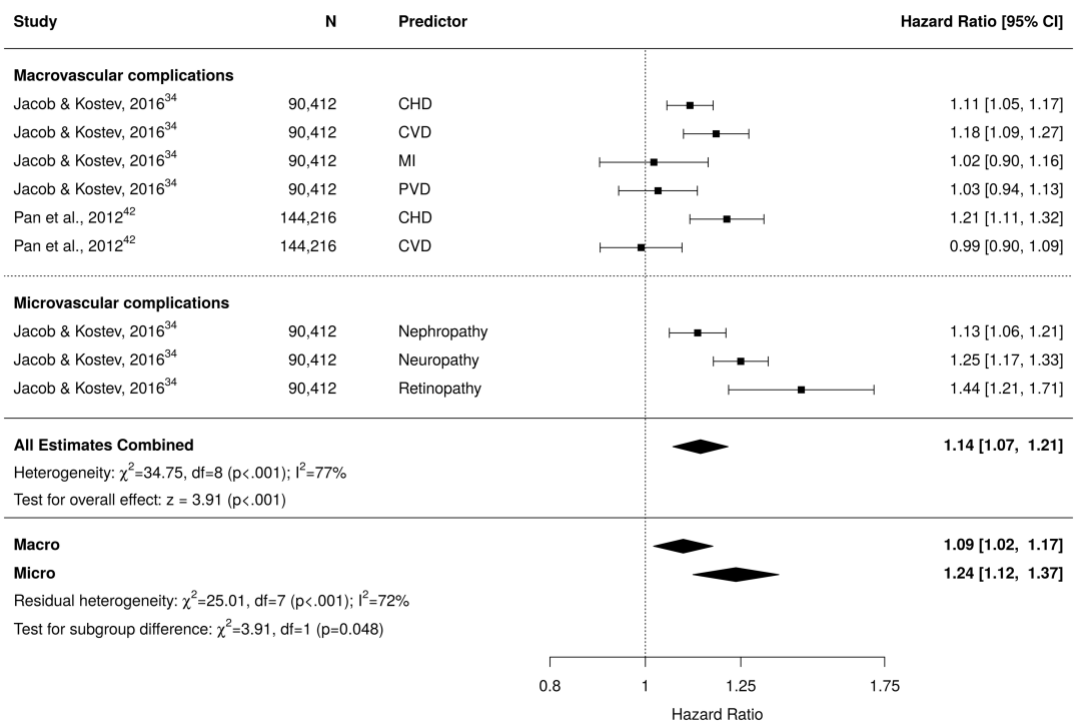
Note: CAD=Coronary artery disease; CHD=coronary heart disease; CVD=cerebrovascular disease; MI=myocardial infarction; PVD=Peripheral vascular disease.

Figure 3. Forest Plot of hazard ratios of longitudinal studies included in the meta-analysis examining associations from baseline diabetes complications, grouped by macrovascular complications and microvascular complications, to incident depression.

Note: CHD=coronary heart disease; CVD=cerebrovascular disease; MI=myocardial infarction; PVD=Peripheral vascular disease.


Identification
Records identified through Embase (n=4885)
Records identified through Medline (n=1629)
Records identified through PsycInfo (n=943)
Records identified through data base searching (n = 7457)
Conference papers, books, dissertations, duplicates removed (n=2866)
Additional records identified through other sources (n=1)
Screening
Records screened (n=4591)
Records excluded (n = 4493)
Eligibility
Full-text articles assessed for eligibility (n = 99)
Full-text articles excluded with reasons (n = 69)
Not focused on diabetes population n=23
Not focused on diabetes complications n=10
Outcome = recurrent foot ulcers n=2
Outcome = cognitive decline/dementia n=4
Outcome = mortality n=5
Other outcomes n=7
No comparison of complications vs no complications n=3
Cross-sectional n=12
Participants were adolescents n=1
Complications to persistent depression n=2
Inclusion
Studies identified (n = 30)
Studies from the same cohort with duplicate information (n=8)
Epidemiology of Diabetes Complication (EDC) n=5
Pathways n=3
Studies included (n = 22)
depression -> complications n=16
complications -> depression n=6
Studies included in the meta-analyses (n=11)
Depression -> complications n=9
Complications -> depression n=2
Studies not included in the meta-analyses (n=11)
Depression -> complications n=7
Complications -> depression n=4


Study
N
Outcome
Hazard Ratio [95% CI]
Macrovascular complications
Black et al., 2003[16] 636 CAD, CVD, Kidney Disease 1.66 [1.20, 2.29]
Clouse et al., 2003[38] 76 CHD, CVD, PVD 5.20 [1.42, 19.11]
Jani et al., 2016[45] 18,453 CHD, CVD 1.20 [1.05, 1.37]
Lin et al., 2010[17] 3,723 CHD, CVD, PVD 1.44 [1.22, 1.70]
Nefs et al., 2015[19] 961 CHD 0.68 [0.29, 1.58]
Novak et al., 2016[31] 933,211 CHD 1.43 [1.39, 1.47]
Novak et al., 2016[31] 933,211 CVD 1.41 [1.38, 1.44]
Scherrer et al., 2011[18] 53,632 CHD 1.37 [1.26, 1.49]
Sullivan et al., 2012[32] 2,053 CHD 1.42 [0.99, 2.04]
Ting et al., 2013[33] 7,835 CHD, CVD, PVD 1.94 [1.31, 2.87]
Microvascular complications
Black et al., 2003[16] 636 Nephropathy, Retinopathy, Neuropathy 3.60 [2.79, 4.65]
Lin et al., 2010[17] 3,723 Nephropathy, Retinopathy, Diabetic Foot Ulcers 1.46 [1.19, 1.79]
Novak et al., 2016[31] 933,211 Nephropathy 1.36 [1.35, 1.37]
Sullivan et al., 2012[32] 2,053 Nephropathy, Retinopathy 0.93 [0.53, 1.63]
All Estimates Combined 1.51 [1.23, 1.86]
Heterogeneity: χ^2=92.30, df=13 (p<.001); I^2=86%
Test for overall effect: z = 3.96 (p<.001)
Macro (without Black et al, 2003) 1.38 [1.30, 1.47]
Micro (without Black et al, 2003) 1.33 [1.25, 1.41]
Residual heterogeneity: χ^2=18.97, df=10 (p=0.041); I^2=47%
Test for subgroup difference: χ^2=18.82, df=1 (p<.001)
0.25 0.5 1 2 4 8
Hazard Ratio


Study
N
Predictor
Hazard Ratio [95% CI]
Macrovascular complications
Jacob & Kostev, 2016[34] 90,412 CHD 1.11 [1.05, 1.17]
Jacob & Kostev, 2016[34] 90,412 CVD 1.18 [1.09, 1.27]
Jacob & Kostev, 2016[34] 90,412 MI 1.02 [0.90, 1.16]
Jacob & Kostev, 2016[34] 90,412 PVD 1.03 [0.94, 1.13]
Pan et al., 2012[42] 144,216 CHD 1.21 [1.11, 1.32]
Pan et al., 2012[42] 144,216 CVD 0.99 [0.90, 1.09]
Microvascular complications
Jacob & Kostev, 2016[34] 90,412 Nephropathy 1.13 [1.06, 1.21]
Jacob & Kostev, 2016[34] 90,412 Neuropathy 1.25 [1.17, 1.33]
Jacob & Kostev, 2016[34] 90,412 Retinopathy 1.44 [1.21, 1.71]
All Estimates Combined 1.14 [1.07, 1.21]
Heterogeneity: χ²=34.75, df=8 (p<.001); I²=77%
Test for overall effect: z = 3.91 (p<.001)
Macro 1.09 [1.02, 1.17]
Micro 1.24 [1.12, 1.37]
Residual heterogeneity: χ²=25.01, df=7 (p<.001); I²=72%
Test for subgroup difference: χ²=3.91, df=1 (p=0.048)
0.8
1
1.25
1.75
Hazard Ratio

Supplementary Text 1. Search criteria Embase

Database: Embase <1974 to 2016 October 05>
Search Strategy:

1 diabetes/ or diabetes mellitus/co, di, px, ep (499874)
2 "diabet*".ti,ab. (707014)
3 1 or 2 (805841)
4 "depression (emotion)"/ or major depression/co, di, px, ep (7361)
5 "depress*".ti,ab. (482519)
6 4 or 5 (483805)
7 diabetes mellitus/ or diabetic angiopathy/ or diabetic cardiomyopathy/ or diabetic foot/ or diabetic hypertension/ or diabetic nephropathy/ or diabetic neuropathy/ or diabetic retinopathy/co, di, px, ep (594007)
8 Diabetes Complications.mp. (3507)
9 ("diabetic angiopath*" or "diabetic cardiomyopath*" or "diabetic foot" or "diabetic hypertension" or "diabetic neuropath*" or "diabetic nephropath*" or "diabetic retinopath*").ti,ab. (60658)
10 7 or 8 or 9 (607118)
11 exp Stroke/co, di, ep (17979)
12 "strok*".ti,ab. (281326)
13 11 or 12 (288429)
14 exp Sexual Dysfunction/co, di, ep (11900)
15 "sexual dysfunction*".ti,ab. (13800)
16 14 or 15 (23491)
17 exp Cerebrovascular disorders/co, di, ep (115603)
18 exp cerebrovascular Disease/co, di, ep (115603)
19 ("cerebrovascular diseas*" or "cerebrovascular disorder").ti,ab. (23494)
20 exp heart infarction/co, di, ep (60551)
21 "myocardial infarction*".ti,ab. (217248)
22 17 or 18 or 19 or 20 or 21 (371363)
23 10 or 13 or 16 or 22 (1165895)
24 3 and 6 and 23 (14603)
25 limit 24 to (human and English language and yr="1980 -Current" and adult <18 to 64 years>) (5259)

Supplementary Text 2. Summary and scoring of the Newcastle-Ottawa scale

SELECTION

Representativeness of the exposed cohort

a) truly representative of the average person with diabetes in the community *
b) somewhat representative of the average person with diabetes in the community *
c) selected group of users e.g. nurses, volunteers
d) no description of the derivation of the cohort

Selection of the non-exposed cohort

a) drawn from the same community as the exposed cohort *
b) drawn from a different source
c) no description of the derivation of the non-exposed cohort

Ascertainment of exposure (depression diagnosis / complications)

a) secure record (e.g. surgical records) *
b) structured interview *
c) written self-report
d) no description

Demonstration that outcome of interest was not present at start of study

a) yes *
b) no

COMPARABILITY

Comparability of cohorts on the basis of the design or analysis

i) study controls for complications/depression at baseline
a) yes *
b) no *
ii) study controls for any additional factor a) yes *
b) no

OUTCOME

Assessment of outcome

a) independent blind assessment *
b) record linkage *
c) self-report
d) no description

Was follow-up long enough for outcomes to occur?

Minimum follow-up time complications 5 years
Minimum follow-up time recurrence foot ulcers 18 months
Minimum follow-up time depression 24 months
a) yes *
b) no

Adequacy of follow up of cohorts

a) complete follow-up - all subjects accounted for *
b) subjects lost to follow up unlikely to introduce bias - small number lost, >80% follow up, or description provided of those lost *
c) follow up rate <80% and no description of those lost
d) no statement

*The Newcastle-Ottawa Scale quality instrument is scored by awarding a point for each answer that is marked with an asterisk. Possible total points are 4 points for Selection, 2 points for Comparability, and 3 points for Outcomes.

Reference: Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. *Ottawa Hosp Res Inst*. 2013;(3):1-4. doi:10.2

Supplementary Table 1A. Depression to macrovascular complications *(Overview of all included studies sorted by publication date in ascending order)*

Author, year, country	Follow-up (years)	Study design and population	Baseline number of participants (mean age, sex, type of diabetes)	Diabetes Duration (mean±SD) [range] years	Depression assessment	Diabetes assessment	Complication assessment	Major findings
Lloyd et al., 1996, USA[20]	4	Prospective cohort study recruited from Children's Hospital of Pittsburg registry of IDDM (Pittsburgh Epidemiology of Diabetes Complications study (EDC))	634 (27 years, 49% women, type 1)	19.0 ± 7.5	BDI	Hospital registry: childhood-onset (<17 years) IDDM and to be on insulin therapy at discharge	CAD: Presence of angina (diagnosed by physician), a history of MI (confirmed by ECG or by review of medical records), or death due to CAD (by death certificate review) during the follow-up period	For men, duration of IDDM, HDL cholesterol and nephropathy were independent predictors of CAD. For women, duration, hypertension, waist-hip ratio, physical activity, and depressive symptomatology were all independent predictors of CAD. Cox Proportional Hazards Model Standardised RR sex x depression=1.60 (SE 0.01) *p*=0.053
Orchard et al., 1999, USA[22]	8	Nested Case-control Study recruited from Children's Hospital of Pittsburg registry of IDDM (Pittsburgh Epidemiology of Diabetes Complications study (EDC))	98: 49 cases + 49 matched controls (34 years, 49% women, type 1)	26.0 ± 6.4	BDI	Hospital registry: childhood-onset (<17 years) IDDM and to be on insulin therapy at discharge	CAD: Presence of angina (diagnosed by physician), a history of MI (confirmed by ECG or by review of medical records), or death due to CAD (by death certificate review) during the follow-up period	Depression, hypertension, and log Ab-OxLDL (antibodies to oxidized LDL) were independent predictors of CAD in multivariate analysis. Cox Proportional Hazards Model Depression: RR=1.5 (95%CI 1.45–1.54)
Forrest et al., 2000, USA[24]	6	Prospective cohort study recruited from Children's Hospital of Pittsburg registry of IDDM (Pittsburgh Epidemiology of Diabetes Complications	658 (28 years, 49% women, type 1)	20	BDI	Hospital registry: childhood-onset (<17 years) IDDM and to be on insulin therapy at discharge	CHD and LEAD: CHD, presence of angina (diagnosed by physician), a history of MI (confirmed by ECG or by review of medical records), or death due to CAD (by death certificate review) during the follow-up period. LEAD, an ankle-to-arm ratio < 0.9 at rest, a history	Hypertension, low HDL cholesterol level, high white cell count, depression, and nephropathy were independent risk factors for CHD (including morbidity and mortality). Depressive symptoms did not predict LEAD. Cox Proportional Hazards Models Total CHD: BDI coefficient = 0.06 (SE 0.02; *p* =0.003) CHD morbidity: BDI coefficient = 0.07 (SE 0.02; *p* = 0.003)

		study (EDC))					of claudication or amputation for vascular cause	
Kinder et al., 2002, USA[25]	10	Prospective cohort study recruited from Children's Hospital of Pittsburg registry of IDDM (Pittsburgh Epidemiology of Diabetes Complications study (EDC))	525 (29 years, 50% women, type 1)	20 [8–37]	BDI	Hospital registry: childhood-onset (<17 years) IDDM and to be on insulin therapy at discharge	CHD: Presence of angina (diagnosed by physician), coronary occlusion greater than 50% by angiography, coronary revascularisation, MI (confirmed by ECG or by review of medical records)	Depressive symptoms predicted CHD in a sample of both men and women with type 1 diabetes who were free of CHD at baseline. Cox Proportional Hazards Model All CHD: HR*=1.29 (95%CI 1.08–1.54) *Univariate
Black et al., 2003, USA[16]	7 5 for "lifetime major depression or dysthymia"	Longitudinal population based study of Mexican Americans residing in the South Western USA (subgroup with diabetes) (Hispanic Established Population for the Epidemiologic study of the Elderly: EPESE)	636 (≥ 65 years, % women n/a, type 2) "No depression" (CESD=0) *n*=79 "Minimal depression" (CESD=1-15) *n*=369 "Minor depression" (CESD≥16) *n*=188 "Lifetime major depression or dysthymia" *n*=52/453	n/a	CES-D≥16 or clinical diagnostic criteria (CIDI), DSM-IV	Self-report	CAD, stroke, kidney disease by self-report	Compared to reference group of people without DM or depression, having T2DM and depression predicted increased incidence of macrovascular complications. Cox Proportional Hazards Models "Minimal depression": HR*=1.56 (95%CI 1.21–2.00) "Minor depression": **HR*=2.40 (1.71–3.36)** "Lifetime major depression or dysthymia": HR*=2.64 (95%CI 1.73–4.04) *Adjusted for age, sex, education, acculturation, marital status
Orchard et al., 2003, USA[23]	10	Prospective cohort study recruited from Children's Hospital of Pittsburg registry of IDDM	603 (28 years, % women n/a, type 1)	19 (7–37)	BDI scores	Hospital registry: childhood-onset (<17 years) IDDM and to be on insulin therapy at discharge	CAD: defined as MI confirmed by hospital records or ECG; angina diagnosed by an physician; angiographically proven stenosis defined as ≥50% blockage, or	Depressive symptoms were an independent risk factor for angina, but did not predict hard CAD events (e.g. myocardial infarction) or total CAD (no data provided). Cox Proportional Hazard Model Angina: HR=1.40 (95%CI 1.06–1.84)

		(Pittsburgh Epidemiology of Diabetes Complications study (EDC))					revascularization; ischemic ECG	
Clouse et al., 2003, USA[38]	6	Prospective study of women diabetic subjects recruited as part of a series of investigations by the National Institutes of Health in Washington	76 (41 years, 100% women, type 1, type 2 [55%]) No depression *n*=60 Major depression *n*=16	Depression 13.1 ± 8.8 No depression 12.2 ± 7.8	Mental Health Diagnostic Interview, DSM-III	National Diabetes Data group criteria	CHD, PVD, cerebrovascular disease (CVD): CHD, based on documented MI or ischemic electrocardiographic changes observed at rest or during an exercise treadmill test. PVD, history of claudication, pulseless lower extremity, or ischemic ulceration of a lower extremity.CVD by transient ischemic attacks or cerebrovascular accident	Major depression was an independent risk factor that accelerated the development of CHD. Depression did not predict PVD or cerebrovascular diseases – data not presented. Cox Proportional Hazard Models HR*=6.67 (95%CI 1.26–35.23) **HR**=5.2 (95%CI 1.4–18.9)** *Univariate **Adjusted for age
Roy et al., 2007a, USA[29]	6	Longitudinal study of African-American people with type 1 diabetes admitted to hospitals in New Jersey	483 (28 years, 60% women, type 1) 449 without evidence of CVD No depression, (BDI ≤ 14) *n*=264 Depression (BDI >14) *n*=51	10.4 ± 8.6	BDI>14	Medical records	CVD: defined as CAD, either angina or MI and stroke by ICD-9 codes and ECG abnormalities	Baseline older age, higher body mass index, higher diastolic blood pressure, proteinuria, retinopathy severity and being depressed were significant and independent risk factors for incidence of any CVD. Of 283 pts without baseline depression 11.7% developed CAD or stroke. Of 94 with baseline depression 19.2% developed CAD or stroke. OR*=1.04 (95%CI 1.001–1.08) *Adjusted for age, diastolic BP, BMI, retinopathy
Lin et al., 2010, USA[17]¶	5	Longitudinal cohort study of primary care people with type 2 diabetes in Western Washington state, USA (Pathways Epidemiology	3,723 (64 years, 48% women, type 2) No depression: *n*=2965 Minor depression: *n*=315	8.8 ± 8.4	PHQ-9 algorithm Minor depression: 2-4 positive symptoms including 1 core symptom	In the preceding 12 months: filled prescription for insulin or an oral hypoglycemic agent, two fasting plasma glucose levels ≥126 mg/dl, two random	MI, stroke, congestive heart failure (CHF), cardiovascular procedures, and revascularization of the lower extremity, deaths due to coronary, cerebrovascular, or peripheral disease: medical records review, ICD-9	Major depression was associated with significantly higher risks of adverse macrovascular outcomes. Macro-vascular events developed in: 702/2,965 without depression 81/315 pts with minor depression 110/443 pts with major depression

		Study) Major depression: *n*=443 Any prior macro-vascular event: Total sample: n=1,042 No depression: n=788 Minor depression: n=108 Major depression: n=146		(depressed mood or loss of interest) Major depression: at least 5 positive symptoms including 1 core symptom	plasma glucose levels ≥200 mg/dl, two outpatient diagnoses of diabetes, or any inpatient diagnosis	coding	Cox Proportional Hazard Models Minor depression: HR*=1.17 (95%CI 0.92–1.47) HR**=1.09 (95%CI 0.86–1.37) HR***=1.11 (95%CI 0.88–1.40) HR****=1.00 (95%CI 0.79–1.27) Major depression: HR*=1.20 (95%CI 0.98–1.47) HR**=1.13 (95%CI 0.92–1.38) **HR***=1.49 (95%CI 1.21–1.83)** HR****=1.25 (95%CI 1.00–1.54) *Unadjusted ** Adjusted for any prior event *** Adjusted for any prior event + demographics **** Fully adjusted (DM duration, DM Tx, height, weight, SDSCA, HbA1c)
Scherrer et al., 2011, USA[18]	7	A cohort of people free of cardiovascular disease at baseline, selected from the Veterans Administration electronic medical records	53,632 (56 years, 12% women of the total sample, type 2) Total baseline sample: N=345,949 MI: n=11,659 No MI: n=334,290 No DM/ No depression: 62.1% of total sample 48.3% of MI 62.6% of No MI No DM/depression 22.4% of total sample 23.0% of MI 22.4% of No MI	Not specified	ICD-9-CM codes	ICDM-9CM codes or a prescription for type 2 diabetes medication	MI and all course mortality: MI identified by ICD-9-CM obtained from Veterans Vital Status File	Compared to people with only diabetes or only major depressive disorder, people with type 2 diabetes and MDD are at increased risk for new-onset MI. Incidence of MI: Pts with no DM or depression: 2.6% Pts with only depression: 3.5% Pts with DM only: 5.9% Pts with DM + depression: 7.4% Cox Proportional Hazard Models No DM/No depression: HR*=1.0 (ref) No DM/Depression: HR*=1.29 (95%CI 1.22–1.37) DM/No depression: HR*=1.33 (95%CI 1.27–1.40) DM/Depression: **HR*=1.82 (95%CI 1.69–1.97)** *Adjusted for age, sex, race, marital status, insurance type

			DM/No depress: 11.8% of total sample 20.7% of MI 11.5% of No MI DM/depression: 3.7% of total sample 8.0% of MI 3.5% of No MI					
Sullivan et al., 2012, USA+ Canada[32]	5	Multicenter randomised trial testing independent effects of two strategies of control of blood glucose, blood pressure, and lipids on CVD in people with type 2 diabetes (Action to Control Cardiovascular Risk in Diabetes Health-Related Quality of Life substudy (ACCORD HRQOL))	2,053 (62 years, 40% women, type 2) Ever depressed: *n*=712 Never depressed: *n*=1,326	10 (median)	PHQ-9≥10	Not reported	Macro vascular composite outcome (major coronary artery disease events, specifically fatal events, nonfatal MI, and unstable angina): Not specified but assessed by objective criteria	Depressive symptoms did not predict macrovascular composite outcome among people with type 2 diabetes. Cox Proportional Hazard Models Major depression: **HR*=1.42 (95%CI 0.99–2.04)** HR**=1.36 (95%CI 0.95–1.95) Minor depression: HR*=1.23 (95%CI 0.85–1.78) HR**=1.23 (95%CI 0.85–1.78) PHQ–9 continuous: HR*=1.02 (95%CI 1.00–1.04) PHQ–9 continuous: HR**=1.02 (95%CI 1.00–1.04) PHQ–9 ≥10: HR*= 1.14 (95%CI 0.88–1.49) PHQ–9 ≥10: HR**= 1.10 (95%CI 0.84–1.44) *Adjusted for demographics, trial, clinical variables **Adjusted for demographics, trial, clinical and behavioural variables
Fickley et al., 2013, USA[21]	22	Prospective cohort study recruited from Children's Hospital of Pittsburg registry of IDDM (Pittsburgh	506 (27 years, 51% women, type 1) Age: No CAD: 26.7 (6.3) Incident CAD:	No incident CAD 17.9 ± 6.6 Incident CAD 23.6 ± 6.9	BDI	Hospital registry: childhood-onset (<17 years) IDDM and to be on insulin therapy at discharge	CAD defined as MI confirmed by hospital records or ECG; coronary artery stenosis, defined as ≥50% blockage, or revascularization; ischemic ECG, angina, diagnosed by a physician; or CAD death	Baseline BDI score predicted incident CAD. BDI at baseline no CAD 5.0 (IQR 2.0–10.0) and incident CAD 6.0 (IQR 3.0–11.0), respectively, *p*=0.01.

		Epidemiology of Diabetes Complications study (EDC))	32.1 (6.5) Sex: No CAD 47.1 (*n*=156) Incident CAD 54.0 (*n*=95)				(determined by a mortality classification committee)	
Ting et al., 2013, China[33]	7	Prospective cohort of Hong Kong Chinese with type 2 diabetes but without CVD at baseline	7,835: (No depression, *n*=7,682, 57 years (median), 53% women and depression *n*=153, 52 years (median), 88% women, type 2)	5 (median) [IQR=9]	Psychiatric diagnosis of depression according to DSM-IV criteria	Hong Kong diabetes registry	CVD defined as CHD and/or stroke and/or peripheral vascular disease: using ICD-9 coding	Major depression showed a 2–3 fold increased risk of incident CVD, notably stroke, in Chinese people with type 2 DM. Total CVD outcomes (CAD, stroke, PVD): No depression *n*=798 Depression *n*=31 Cox Proportional Hazard Models HR*=1.68 (95%CI 1.17–2.40) **HR**=1.94 (95%CI 1.31–2.86)** HR***=2.18 (95% CI 1.45–3.27) *Unadjusted Model **Model adjusted for age, sex, smoking status, duration of DM, BMI, BP, HbA1c, lipids ***Model adjusted for previous model + DM treatment
Nefs et al., 2015, The Netherlands[19]		Prospective cohort study of people with type 2 diabetes in primary care in the South of the Netherlands (DiaDDZoB study)	961 (No depression *n*=848; depression *n*=113); (age n/a, 51% women; type 2)	4.8 (mean, ± 1.3)[0.04–5.4}	EPDS	Formal diagnosis of type 2 diabetes by General Practitioner (either a fasting glucose concentration of > 6.9 mmol/l in venous plasma or > 6.0 mmol/l in capillary blood on two separate days, or an arbitrary glucose level > 11.0 mmol/l in the presence of the classic	Hospitalisation for incident cardiovascular event from PHARMO's hospitalisation database	Depression did not increase the risk of hopsitalisations for cardiovascular events. Total CV events: No depression *n*=72 Depression *n*=6 Cox Proportional Hazard Models HR*=0.62 (95%CI 0.27–1.43) **HR**=0.68 (95%CI 0.29–1.56)** *Unadjusted Model **Model adjusted for age and sex

						hyperglycemia symptoms), and receiving treatment for diabetes		
Jani et al., 2016, UK[45]	4	Cohort recruited from two health boards in the West of Scotland that serve a population of approximately 1.8 million	18,453 (69 years, 41.8% women, n/a)	n/a	HADS-D>7	People in a family practice disease register with a diagnosis of at least one of CHD, diabetes, or stroke	ICD-10 coding: 1. Admission due to MI 2. Admission due to stroke 3. Admission due to heart failure (HF) 4. Death due to CV causes Major adverse CV outcome (CV mortality or admission due to MI/stroke/HF) was used as the composite outcome variable.	Depression predicted adverse macrovascular outcome in people with diabetes. Major adverse cardiovascular outcome developed in: 1,808/18,452 participants (with or without depression) HR*=1.33 (95%CI 1.19–1.48) **HR**=1.20 (95%CI 1.05–1.36)** HR***=1.21 (95%CI 1.05–1.38) * Unadjusted ** Adjusted for body mass index, total cholesterol, age, gender, socio-economic status, number of co-morbid conditions, and initiation of anti-depressants. *** Adjusted for body mass index, total cholesterol, age, gender, socio-economic status, number of co-morbid conditions, initiation of anti-depressants, and HbA1c
Novak et al., 2016, USA[31]	6	Cohort of US veterans with diabetes. Data from the Racial and Cardiovascular Risk Anomalies in CKD (RCAV) study	933,211 (no depression *n*=592,405; depression *n*= 340,806);(64 years ± 11; 3% women; type 1 + type 2)	n/a	ICD-9-CM codes for depression or receiving antidepressant medication	ICD-9 codes for diabetes, receiving any type of oral anti diabetic treatment or insulin, or having at least one measured HbA1c >6.6% (46 mmol/mol)	Incident CHD defined as defined as the composite outcome of a first occurrence of an ICD-9-CM or Current Procedural Terminology code for acute myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention Incident stroke defined as first occurrence of ICD-9-CM codes for ischemic stroke	Depresion was associated with increased risk for both CHD events and stroke. Cox Proportional Hazard Models Stroke: HR*=1.43 (95%CI 1.39–1.46)† **HR**=1.46 (95%CI 1.50–1.43)†** HR***=1.32 (95%CI 1.28–1.36) CV event: HR*=1.49 (95%CI 1.46–1.52)† HR**=1.43 (95%CI 1.38–1.44)† HR***=1.22 (95%CI 1.19–1.24) *Unadjusted model **Model 1 adj for age, sex, race/ethnicity ***Model 4 adj for age, sex, race/ethnicity,

								marital status, baseline eGFR, comorbidities at baseline (hypertension, CVD, congestive heart failure, cerebrovascular disease, peripheral vascular disease, lung disease, dementia, rheumatic disease, malignancy, HIV/AIDS, and PTSD), use of statins or antihypertensive medications, BMI, and serum albumin level †Data were obtained from the authors
Ismail et al., 2017, UK[36]	2	People with diabetes from inner city primary care clinics, recruited within 6 months of diabetes diagnosis	1,651 (56.2 years, 44.9% women, type 2)	< 6 months	PHQ-9	Medical records	Any MI, coronary artery bypass graft (CABG),stroke or carotid/limb revascularization or amputation: derived from medical records	Depressive symptoms predicted macrovascular composite outcome among people with type 2 diabetes. Macrovascular events developed in: 30/1,077 pts without depression 10/170 pts with depressive symptoms OR*=2.18 (95%CI 1.05–4.55) OR**=2.78 (95%CI 1.19–6.49) OR***=2.29 (95%CI 0.88–5.95) *Unadjusted ** Adjusted for age, sex, non-white ethnicity, baseline BMI, baseline systolic BP, baseline smoking status, baseline serum cholesterol, baseline HbA1c, prescription of oral hypoglycaemic medication at 2 years, and prescription of insulin at 2 years *** Fully adjusted for age, sex, non-white ethnicity, baseline BMI, baseline systolic BP, baseline smoking status, baseline serum cholesterol, baseline HbA1c, prescription of oral hypoglycaemic medication at 2 years, prescription of insulin at 2 years and baseline IL-1RA concentration (natural log-transformed)

Supplementary Table 1B. Depression to microvascular complications *(Overview of all included studies sorted by publication date in ascending order)*								
Author, year, country	**Follow-up (years)**	**Study design and population**	**Number of participants (mean age, sex, type of diabetes)**	**Diabetes Duration (mean±SD) [range]**	**Depression assessment**	**Diabetes assessment**	**Complication: assessment**	**Major findings**
Black et al., 2003, USA[16]	7 5 for "Lifetime major depression or dysthymia"	Longitudinal population based study of Mexican Americans residing in the South Western USA (EPESE)	636 out of 2,830 (≥ 65 years, 59% women, type 2) "No depression" (CESD=0) *n*=79 "Minimal depression" (CESD=1-15) *n*=369 "Minor depression" (CESD≥16) *n*=188 "Lifetime major depression or dysthymia" *n*=52/453	n/a	CES-D≥16 or clinical diagnostic criteria (CIDI), DSM-IV	Self-report	Nephropathy, retinopathy, neuropathy: based on self-report	Compared to reference group of people without DM or depression, having T2DM and depression predicted increased incidence of microvascular events. Cox Proportional Hazard Models "Minimal depression": HR*=2.43 (95%CI 1.90–3.14); "Minor depression": **HR*=8.63 (95%CI 5.40–13.79)** "Lifetime major depression or dysthymia": HR*=11.32 (95%CI 8.76–15.43) *Adjusted for age, sex, education, acculturation, marital status
Roy et al., 2007b, USA[30]	6	Longitudinal study of African-American people with type 1 diabetes admitted to hospitals in New Jersey	483 (BDI>14 *n*=51, 33 years 61% women and BDI≤14 *n*=264, 29 years, 57% women, type 1)	11.0 ± 8.5	BDI>14	Medical records	Retinopathy: by color fundus photography graded in a blinded fashion using the Airlie House classification	Depression is significantly associated with poor glycaemic control and higher progression of proliferative diabetic retinopathy in African Americans with type 1 diabetes. Diabetes retinopathy: OR*=3.04 (95%CI 1.39–6.65) OR**=2.44 (95%CI 1.01–5.88) Proliferative diabetic retinopathy: OR*=3.41 (95%CI 1.64–7.11) OR**=3.19 (95%CI 1.30–7.87) *Univariate ** Adjusted for glycosylated Hb (per 1%), diabetes duration (per 1 year) and Systemic

								hypertension
Gonzalez et al, 2010, UK + USA[41]	1.5	A prospective cohort study of people with diabetes at high risk for foot ulceration attending three sites for diabetes treatment in the UK or USA	333 (62 years, 29% women, type 1 and type 2 [73%])	17.0 ± 11.5	HADS	Medical records	Defined as a full-thickness skin break below the malleolus (foot-ankle junction): History and follow-up evaluations of foot ulcer by self-report, baseline and each follow-up visit by medical examination	Depression predicted the risk of developing first foot ulcers, but not recurrent diabetic foot ulcers. Cox Proportional Hazard Model Incident foot ulcers HR*=1.68, 95% (95%CI 1.20–2.35) Recurrent foot ulcers HR*=0.88 (95%CI 0.61–1.27) *Adjusted for Retinopathy, VPT, foot self-care
Lin et al., 2010, USA[17]	5	Longitudinal cohort study of people with type 2 diabetes in primary care clinics in Western Washington state, USA (Pathways Epidemiology Study)	3,723 (64 years, 48% women, type 2) No depression: *n*=2,965 Minor depression: *n*=315 Major depression: *n*=443 Any prior micro-vascular event: Total sample: *N*=750 No depression: *n*=580 Minor depression: *n*=77 Major depression: *n*=93	8.8 ± 8.4	PHQ-9 algorithm Minor depression: 2-4 positive symptoms including 1 core symptom (depressed mood or loss of interest) Major depression: at least 5 positive symptoms including 1 core symptom	In the preceding 12 months: filled prescription for insulin or an oral hypoglycemic agent, two fasting plasma glucose levels ≥126 mg/dl, two random plasma glucose levels ≥200 mg/dl, two outpatient diagnoses of diabetes, or any inpatient diagnosis	End-stage renal disease, low vision or blindness, proliferative retinopathy or photocoagulation procedures for diabetes, and foot ulcers: using medical records review, ICD-9 coding	Major depression was associated with significantly higher risks of adverse microvascular outcomes. Micro-vascular events developed in: 394/2,965 pts without depression 59/315 pts with minor depression 80/443 pts with major depression Cox Proportional Hazard Models Minor depression: HR*=1.54 (95%CI 1.16–2.03) HR**=1.49 (95%CI 1.13–1.97) HR***=1.48 (95%CI 1.11–1.95) HR****=1.31 (95%CI 0.98–1.74) Major depression: HR*=1.48 (95%CI 1.16–2.03) HR**=1.47 (95%CI 1.15–1.87) **HR***=1.67 (95%CI 1.30–2.15)** HR****=1.36 (95%CI 1.05–1.76) *Unadjusted ** Adjusted for any prior event *** Adjusted for any prior event + demographics **** Fully adjusted (any prior event, demographics, DM duration, DM Tx, height, weight, SDSCA, HbA1c)

Williams et al., 2010, USA[27]	4.1	Longitudinal cohort study of people with type 2 diabetes without prior diabetic foot ulcers or amputations from primary care clinics in Western Washington state, USA (Pathways Epidemiology Study)	3,474 (64 years, 48% women, type 2)	8.5 ± 8.2	PHQ-9	In the preceding 12 months: filled prescription for insulin or an oral hypoglycemic agent, two fasting plasma glucose levels ≥126 mg/dl, two random plasma glucose levels ≥200 mg/dl, two outpatient diagnoses of diabetes, or any inpatient diagnosis	Diabetic foot ulcer: first screened using ICD-9 diagnosis codes; diagnosis confirmed by chart review	Compared to people without depression, people with major depression had a 2–fold increase in the risk of incident diabetic foot ulcers, whereas minor depression was not associated with incident diabetic foot ulcers. Cox Proportional Hazard Models Major depression HR*=2.00 (95% CI, 1.24–3.25) Minor depression HR*=1.37 (95% CI, 0.77–2.44) *Fully adjusted model: sociodemographic characteristics, medical comorbidity, glycosylated hemoglobin, diabetes duration, insulin use, number of diabetes complications, body mass index, smoking status, and foot self-care
Sieu et al., 2011, USA[26]	5	Longitudinal cohort study of people with type 2 diabetes from primary care clinics in Western Washington state, USA (Pathways Epidemiology Study)	2,359 (64 years, 48% women, type 2)	8.1 ± 8.1	PHQ-9	In the preceding 12 months: filled prescription for insulin or an oral hypoglycemic agent, two fasting plasma glucose levels ≥126 mg/dl, two random plasma glucose levels ≥200 mg/dl, two outpatient diagnoses of diabetes, or any inpatient diagnosis	Incident retinopathy: retinal evaluation by an optometrist or an ophthalmologist and had ICD-9 codes	People with diabetes and comorbid depression had a significantly higher risk of developing diabetic retinopathy. Logistic Regression Model OR*=1.026 (95%CI 1.002–1.051) Depressive symptoms were associated with time to incident retinopathy. Cox Proportional Hazard Model HR*=1.025 (95%CI 1.009–1.041) *Adjusted for length of follow-up, sociodemographic characteristics, baseline clinical characteristics, and health behaviours
Sullivan et al., 2012, USA + Canada[32]	5	Multicenter randomized trial testing the effects of two strategies of control of blood glucose, blood pressure, and lipids on	2,053 (62 years, 40% women, type 2) Ever depressed: *n*=712	10 (median)	PHQ-9 and PHQ-9≥10	Not reported	Composite micro vascular outcome (fatal or nonfatal renal failure or retinal photocoagulation or vitrectomy for diabetic retinopathy): Not specified Assessed by objective	Depressive symptoms did not predict microvascular composite outcome among people with type 2 diabetes. Cox Proportional Hazard Models Major depression: **HR*=0.93 (95%CI 0.53–1.62)**

		CVD in people with diabetes (Action to Control Cardiovascular Risk in Diabetes Health-Related Quality of Life substudy; ACCORD HRQOL)	Never depressed: *n*=1,326				criteria	HR**=0.97(95%CI 0.56–1.70) Minor depression: HR*=1.14 (95%CI 0.70–1.85) HR**=1.14 (95%CI 0.70–1.86) PHQ-9 continuous: HR*=1.01 (95%CI 0.98–1.04) PHQ-9 continuous: HR**=1.01 (95%CI 0.99–1.04) PHQ-9 ≥10: HR*=1.27 (95%CI 0.90–1.80) PHQ-9 ≥10: HR**=1.31 (95%CI 0.93–1.86) *Adjusted for demographic, trial, clinical variables **Adjusted for demographic, trial, clinical and behavioural variables
Yu et al., 2015, USA[28]	10	Longitudinal cohort study of people with type 2 diabetes from primary care clinics in Western Washington state, USA (Pathways Epidemiology Study)	3,886, 63 years, 48% women, type 1 + type 2) (No depression *n*=3,111; major depressive symptoms *n*=448; minor depressive symptoms *n*=327)	6.3 [3–15]	PHQ-9≥10 and major depression using PHQ-9 algorithm	Group Health Diabetes Registry	ESRD requiring dialysis or kidney transplant based on ICD-9 codes	Major but not minor depressive symptoms were associated with a higher risk of incident end stage renal disease. Cox Proportional Hazard Models HR*=2.31 (95%CI 0.71–2.89) HR**=1.90 (95%CI 1.09–3.32) HR***=1.85 (95%CI 1.02–3.33) *Unadjusted **Model 1: Adjusted for age, sex, race/ethnicity, marital status, education level, smoking status, body mass index, duration of diabetes, hemoglobin A1c, eGFR, presence of baseline microalbuminuria, hypertension, and ACEI/ARB use ***Model 2: Model 1 + diabetes self-care activities
Novak et al., 2016, USA[31]	6	Cohort of US veterans within diabetes. Data from the Racial and Cardiovascular Risk Anomalies	933,211 (no depression *n*=592,405; depression *n*= 340,806; 64 years ± 11; 3% women; type 1 + type 2)	n/a	ICD-9-CM codes for depression or receiving antidepressant medication	ICD-9 codes for diabetes, receiving any type of oral anti diabetic treatment or insulin, or having at least	Incident CKD was defined as having two eGFR levels <60 mL/min/1.73 m^2 separated by ≥ 90 days after the enrollment period and a >25% decline from baseline eGFR	Depression was associated with increased risk for chronic kidney disease in people with diabetes. Cox Proportional Hazard Models

		in CKD (RCAV) study				one measured HbA1c >6.6% (46 mmol/mol)		HR*=1.19 (95%CI 1.18–1.21) **HR**=1.36 (95%CI 1.35–1.38)** † HR***=1.18 (95%CI 1.17–1.20) *Unadjusted model **Model 1 adj for age, sex, race/ethinity ***Model 4 adj for age, sex, race/ethnicity, marital status, baseline eGFR, comorbidities at baseline (hypertension, CVD, congestive heart failure, cerebrovascular disease, peripheral vascular disease, lung disease, dementia, rheumatic disease, malignancy, HIV/AIDS, and PTSD), use of statins or antihypertensive medications, BMI, and serum albumin level †Data were obtained from the authors
Iversen et al., 2015, Norway[43]	11	Community based longitudinal study including residents of Nord-Trøndelag county (the Nord-Trøndelag Health Study)	1,415 out of 36,031 (55 years, 49% women, type n/a)	5.0 [0–12]	HADS≥8 or ≥11	Self-report followed by fasting blood glucose sample	Self-report	Symptoms of depression at baseline were associated with an increased risk of a diabetic foot ulcer in a dose response manner during this 11-year follow-up. Where HADS-D was measured as a continuous variable, results showed an approximately 10% increase for each unit increase in HADS-D. Logistic Regression Analyses Compared to people with a HADS-D score <8, HADS-D score 8–10: OR*=1.95 (95%CI 1.02–3.74) HADS-D scores ≥ 11: OR*=3.06 (95%CI 1.24– 7.54) HADS-D as a continuous variable: OR*=1.11 (95% CI 1.04–1.18). *Adjusted for age, sex, and serum glucose
Ismail et al., 2017, UK[36]	2	People with diabetes from Inner city primary care clinics, recruited within 6 months of	1,651 (56.2 years, 44.9% women, type 2)	< 6 months	PHQ-9	Medical records	Neuropathy: assessed clinically at each study visit by neurothesiometry vibration perception threshold ≥25 V Nephropathy, retinopathy:	Depressive symptoms did not predict microvascular composite outcome among people with type 2 diabetes. Microvascular events developed in: 333/1,155 pts without depression

		diabetes diagnosis					derived from medical records	55/179 pts with depressive symptoms OR*=1.10 (95%CI 0.78–1.54) OR**=1.33 (95%CI 0.90–1.96) OR***=1.32 (95%CI 0.85–2.05) *Unadjusted ** Adjusted for age, sex, non-white ethnicity, baseline BMI, baseline systolic BP, baseline smoking status, baseline serum cholesterol, baseline HbA1c, prescription of oral hypoglycaemic medication at 2 years, and prescription of insulin at 2 years *** Fully adjusted for age, sex, non-white ethnicity, baseline BMI, baseline systolic BP, baseline smoking status, baseline serum cholesterol, baseline HbA1c, prescription of oral hypoglycaemic medication at 2 years, prescription of insulin at 2 years and baseline IL-1RA concentration (natural log-transformed)
Trento et al., 2017, Italy[35]	8	Observational prospective study of people with tyoe 2 diabetes were enrolled in an	498 (477 where baseline fundus photos were available; age n/a, % women n/a, type 2)	n/a	Zung Self Rating Scale >60	n/a	Fundus examination was by 2-field, 45° digital colour photography, Retinopathy was classified as absent if corresponding to Early Treatment Diabetic Retinopathy Study (ETDRS) standard 10, mild if doubtful or ETDRS = 20, and moderate or more severe if ETDRS ≥35	Depressive symptoms were not associated with higher risks of retinopathy. No data provided.

Supplementary Table 1C. Complications to depression *(Overview of all included studies sorted by publication date in ascending order)*

Author, year, country	Follow-up (years)	Study design and population	Number of participants (mean age, sex, type of diabetes)	Diabetes Duration (mean±SD) [range]	Depression assessment	Diabetes assessment	Complication: assessment	Major findings
Katon et al., 2009, USA[40]	5	Longitudinal cohort study of	2,759 (55% age > 60 years, 49%	9.0 ± 6.0	PHQ-9 (dichotomous: 5	In the preceding 12 months: filled	Macro- or microvascular events or coronary,	Macrovascular events or procedures (with the exception of stroke) were significant

		people with type 2 diabetes from primary care clinics in Western Washington state, USA (Pathways Epidemiology Study)	women, type 1 and type 2 [95%])		to 9 or ≥ 10 and a continuous severity score)	prescription for insulin or an oral hypoglycemic agent, two fasting plasma glucose levels ≥126 mg/dl, two random plasma glucose levels ≥200 mg/dl, two outpatient diagnoses of diabetes, or any inpatient diagnosis	cerebrovascular or peripheral vascular procedures: were derived from automated data ICD-9 and CPT codes	predictors of depression, whereas microvascular events were not. Major depressive symptoms developed in: 20/202 pts who had a coronary procedure 17/393 pts who had retinopathy 33/550 pts who had nephropathy Logistic Regression Analyses Coronary procedures: OR*=1.92 (95%CI 1.14–3.25) Stroke: OR*=1.75 (95%CI 0.83–3.67) No. of macrovascular events or procedures: OR*=1.39 (95%CI 1.02–1.88) Retinopathy: OR*=0.69 (95%CI 0.40–1.21) Nephropathy: OR*=1.06 (95%CI 0.65–1.71) No. of microvascular events: OR*=0.88 (95%CI 0.64–1.21) *Adjusted for non-response probability and PHQ-9 score groups at baseline
Vileikyte et al., 2009, UK + USA[39]	1.5	A prospective cohort study of people with diabetes and diabetic peripheral neuropathy attending three sites for diabetes treatment in the UK or USA	338 (61 years, 29% women, type 1 and type 2 [73%])	Not specified	HADS	Not specified	Diabetic peripheral neuropathy: severity defined as vibration perception threshold >25V and neuropathy disability score >3; neuropathy symptoms assessed by the Neuropathy and Foot Ulcer-specific quality of Life Instrument (NeuroQol)	Neuropathy was a risk factor for depressive symptoms because it generates pain and unsteadiness. Multivariate Regression Model β*=.56 (p<0.001) β**=.56 (p<0.001) *Model adjusted for baseline HADS-D and demographic/disease variables. **Model 5 adjusted for baseline HADS-D, demographic/disease variables, baseline DPN severity, baseline DPN symptoms, and change in DPN symptoms
Pan et al., 2012, Taiwan[42]	8	Population-based follow-up study of elderly people.	144,216 (72.5 years, 49.5% women, type n/a)	0 years	ICD-9-CM criteria	ICD-9-CM criteria	ICD-9-CM criteria	Macrovascular complications increased the risk of depression onset, with a larger number of complications predicting higher risk of

								depression onset. Depression developed in: 6,124/119,040 pts without complications 541/12,996 pts with stroke 678/12,488 pts with CVD Cox Proportional Hazard Models Stroke: HR*=1.16 (95%CI 1.06–1.27) **HR**=0.99 (95%CI 0.90–1.09)** HR***=0.99 (95%CI 0.90–1.09) CVD: HR*=1.36 (95%CI 1.26–1.47) **HR**=1.21 (95%CI 1.11–1.32)** HR***=1.13 (95%CI 1.04–1.23) *Unadjusted **Model 1 adjusted for age, sex, urbanization status, major illness, and other macrovascular complications / hip fracture ***Model 2 adjusted for Model 1 + number of outpatient visits during 2000-2001
Jacob & Kostev, 2016, Germany[34]	1–10	People with newly diagnosed type 2 diabetes, identified through General Practitioner databases	90,412 (65.5 years, 49.8% women, type 2)	Newly diagnosed	ICD-10	ICD-10	ICD-10	Incident depression was predicted by the following complications: Retinopathy **HR*=1.44 (95%CI 1.21–1.70)** Neuropathy **HR*=1.25 (95%CI 1.17–1.33)** Nephropathy **HR*=1.13 (95%CI 1.06–1.21)** CHD **HR*=1.11 (95%CI 1.05–1.17)** Stroke **HR*=1.18 (95%CI 1.09–1.27)** **But** not predicted by: peripheral vascular disease **HR*= 1.03 (95%CI 0.94-1.13)**† myocardial infarction, **HR*=1.02 (95%CI 0.90-1.16)**† *Multivariate Cox proportional hazards models, adjusted for sex, private insurance, diabetes complications, co-diagnoses and

								prescriptions. †Data were obtained from the authors
Bell et al., 2017, Puerto Rico[44]	4	Longitudinal population-based sample of adults aged 60 years and over for the Puerto Rican Elderly: Health Conditions study (PREHCO)	480 (69.12 years, 59.8% female, type n/a)	n/a	GDS	Self-report	Self-report: Diabetes-related complications were measured as a summed index score of history of problems with circulation, vision, foot sores, amputations, and kidney disease due to diabetes (range 0–4)	Diabetes-related complications were related to greater odds of incident depressive symptoms. OR*=1.46 (95%CI 1.14–1.86) *Logistic regression model that included age, gender, education, vascular comorbidity, diabetes complications, cognitive decline, and baseline cognitive performance.
Deschênes et al., 2017, Canada[37]	5	Prospective cohort study from a community sample in Montreal, Canada	1,314 (age n/a, 52.2% women, type 1 and type2)	n/a	PHQ-9 algorithm	Self-report	Self-report	The number of diabetes complications at baseline was associated with greater risk of elevated depressive symptoms. Macrovascular complications were associated with higher risk of depression, whereas within microvascular symptoms an association was found for neuropathy, but not foot problems or eye problems. Depression developed in: 34/429 pts without complications 66/338 pts with CAD 43/163 pts with CVD 89/537 pts with PVD 71/374pts with neuropathy 13/79 pts with foot problems 37/260 pts with eye problems CAD: RR*=1.85 (95%CI 1.39–2.46) RR**=1.76 (95%CI 1.32–2.35) CVD: RR*=2.41 (95%CI 1.78–3.27) RR**=2.22 (95%CI 1.59–3.10) PVD: RR*=1.61 (95%CI 1.21–2.13) RR**=2.36 (95%CI 1.00–1.83) Neuropathy: RR*=2.82 (95%CI 1.37–2.41) RR**=1.65 (95%CI 1.22–2.23) Foot problems:

								RR*=1.30 (95%CI 0.78–2.19) RR**=1.10 (95%CI 0.63–1.92) Eye problems: RR*=1.14 (95%CI 0.81–1.59) RR**=1.05 (95%CI 0.72–1.53) *Unadjusted **Model 2 adjusted for age, sex, ethnicity, education, marital status, BMI category, smoking frequency, insulin use within the past month, and self-rated diabetes control

Ab-OxLDL=antibody to oxidized low-density lipoprotein; BDI=Beck's depression inventory; BMI=body mass index; BP=blood pressure; CABG=coronary artery bypass graft; CAD=coronary artery disease; CESD=center for epidemiologic studies depression; scale; CHD=coronary heart disease; CHF=congestive heart failure; CI=confidence interval; CIDI=Composite International Diagnostic Interview; CKD=chronic kidney disease; CPT= current procedural terminology; CVD=cerebrovascular disease; DM=diabetes mellitus; DPN=diabetic peripheral neuropathy; *DSM-III*=Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition; *DSM-IV*=Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; ESRD=end stage renal disease; HADS=hospital anxiety and depression scale; HbA1c= glycated hemoglobin; HDL=high density lipoprotein; HR=hazard ratio; ICD-9=international statistical classification of diseases and related health problems; IDDM=insulin dependent diabetes mellitus; LDL=low density lipoprotein; LEAD=lower-extremity arterial disease; MDD=major depressive disorder; MI=myocardial infarction; n/a= not available; OR=odds ratio; PHQ-9=Patient Health Questionnaire-9; PTSD=post traumatic stress disorder; PVD=peripheral vascular disease; RR=relative risk; SDSCA=summary of diabetes self-care activities; SE=standard error; Tx=treatment

Results in **BOLD** represent the models selected for the meta-analysis.